PATENTS
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Turski *et al.*	Art Unit:	1646
Serial No.:	09/746,662	Examiner:	Ruixiang Li
Filing Date:	December 22, 2000		
Title:	**Treatment of Demyelinating Disorders**		

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CERTIFICATION UNDER 37 C.F.R. § 1.8(a)

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RCE (MD) 4/2/04
Maureen DiVito
Maureen DiVito

DECLARATION OF TERENCE SMITH UNDER 37 C.F.R. § 1.132

Dear Sir:

I, Terence Smith declare as follows:

1. I currently hold the position of Head of Pharmacology at Eisai London Research Laboratories Ltd., which is the assignee of the above-referenced patent application ("the Application"). I have worked, initially performing and latterly supervising, research in the field of multiple sclerosis, particularly animal models of the disease, since obtaining my Ph.D. in pharmacology in 1992. My professional experience, educational background, professional activities, and publications are

detailed in the *curriculum vitae* attached hereto as Exhibit A. In addition, similar details are included for the co-inventor, Prof. Dr. Lechoslaw Turski, attached hereto as Exhibit B.

2. As one of the inventors, I have personal knowledge of the invention disclosed and claimed in the Application. I signed a previous Declaration dated August 28, 2003 addressing references cited against the Application.

3. It has been brought to my attention that, following submission of my previous Declaration, in an Advisory Action dated September 30, 2003, the Examiner maintained the rejection of claims 21-22 and 24-25 of the Application under 35 U.S.C. § 103(a) as allegedly being obvious over Shishikura *et al.*, U.S. Patent No. 6,133,258 ("Shishikura") in view of Csuzdi *et al.*, WO 97/28163 ("Csuzdi"), and the rejection of claims 23, 29-30, and 38 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Shishikura in view of Csuzdi and Prineas *et al.*, "Demyelinating Diseases," in Greenfield's Neuropathology, 813-896 (1997).

4. I reviewed the cited references and described my understanding regarding their teachings in my previous Declaration dated August 28, 2003. Below is a further explanation of my understanding of the teachings of the primary reference, Shishikura.

5. Shishikura deals with kainic acid neuronal excitoxicity and protection against it. The reference describes pyridothiazine derivatives that provide potent inhibition of kainic acid neurotoxicity and anticonvulsant effect against seizure, and therefore are useful as agents for treating neurological disorders, including multiple sclerosis (*see, e.g.*, column 2, lines 39-59; column 15, lines 43-53).

6. Shishikura uses the effectiveness of pyridothiazine derivatives against seizures and against kainic acid excitotoxicity, which do not belong to the symptomatology of demyelinating disorders, as evidence for usefulness in the treatment of multiple sclerosis. Multiple sclerosis is included because its symptomatology includes spasticity (which is not necessarily associated with other demyelinating disorders), and AMPA antagonists were known to have muscle relaxant

activity. Shishikura does not recognize that multiple sclerosis is a demyelinating disorder, and does not claim usefulness for therapy of such disorders.

7. Our Application is directed to the therapy of demyelination and the resulting cell death in demyelinating disorders, rather than direct neuroprotection against excitotoxicity induced by kainic acid or glutamate in neurological disorders as disclosed by Shishikura.

8. There is no known relationship between excitotoxicity and cell death due to demyelination. The mechanisms leading to demyelination are not known, and the literature does not teach that signs of excitotoxic cell death are seen in human tissue or tissue from animal models of demyelinating disorders (*e.g.*, EAE models).

9. Therefore, it is NOT OBVIOUS that any compound which protects cells against excitotoxicity induced by kainic acid or against seizures as disclosed in Shishikura may be useful in therapy of demyelinating disorders, including multiple sclerosis. Notably, Shishikura does not mention demyelinating disorders, since at that time it was NOT OBVIOUS to the authors that the compounds claimed are useful for therapy of demyelinating disorders. Indeed, by using multiple sclerosis as an example of a neurological disorder and not using the term "demyelinating disorders" Shishikura itself provides evidence that it was not obvious for a person of ordinary skill in the art to suspect usefulness of AMPA antagonists in therapy of demyelinating disorders. Since it is NOT OBVIOUS that an action against seizures and kainic acid neurotoxicity can be useful in therapy of demyelinating disorders, Shishikura did not claim usefulness of pyridothiazine derivatives against demyelinating disorders.

10. In sum, it simply is NOT OBVIOUS that a person of ordinary skill in the art could conclude from Shishikura's disclosure of the usefulness of pyridothiazine derivatives in treatment of "Huntington's chorea, Parkinson's disease ... and multiple sclerosis" due to "inhibitory action against kainic acid neurotoxicity and anticonvulsant effect for ... seizure" (column 15, lines 43-53) that such agents are useful in therapy of demyelinating disorders.

11. I have been informed that, in the Advisory Action dated September 30, 2003, the Examiner stated that the argument that Dr. Turski and I were the first to recognize the glutamate ionotropic AMPA receptor as a target for the treatment of demyelinating disorders is not persuasive because our work was published in Nature Medicine in 2000, which is after the prior art date of Shishikura. The Examiner's comment merely reemphasizes my statements above and in my previous Declaration. If the work described in our Application was first published in Nature Medicine in 2000, then Shishikura could not disclose or suggest the use of an AMPA receptor inhibitor for treating disorders induced by demyelination. The only teaching in Shishikura relates to the use of an AMPA receptor inhibitor for treating a neurological disorder caused by neurotoxicity. Information regarding the effect of the AMPA receptor on demyelination was only available after the prior art date of Shishikura, as acknowledged by the Examiner.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: _____
Terence Smith

Dated: 25th March 2004

EXHIBIT A

CURRICULUM VITAE: TERENCE SMITH

DATE OF BIRTH: 13th October 1964 **NATIONALITY:** British

ADDRESS (home): 4 The Old School, Norfolk Street, Cambridge, CB1 2LE UK
Telephone: 0044 (0)1223 323 524
e-mail: woodrow.smith@btopenworld.com

ADDRESS (work): Eisai London Research Laboratories Limited
Bernard Katz Building, University College London
Gower Street, London, WC1E 6BT UK
Telephone: 0044 (0)20 7413 1145
e-mail: Terence_Smith@eisai.net

CURRENT EMPLOYMENT

August 1997 – present:
Head of Pharmacology, Eisai London Research Laboratories, London.
In 1992 the London laboratories of Eisai, a leading Japanese pharmaceutical company, were established at UCL with the specific aim of developing novel therapies for CNS degenerative disease. I joined the company in 1997 to expand the portfolio of *in vivo* models of CNS disease. Under my guidance, models of the human demyelinating disease, multiple sclerosis (MS), were established and utilised in the drug screening process. During the past four years, a drug finding project, germinating from the exchange of ideas between London and Tsukuba (Japan), has flourished and now involves a score of researchers including chemists, cell biologists and pharmacologists. The fruition of this work was published in Nature Medicine (January 2000) and Phase I clinical studies were successfully completed September 2002. Phase IIa studies are currently on-going (completion anticipated Autumn 2003).

PREVIOUS EMPLOYMENT

October 1991 – July 1997:
Post Doctoral Research Scientist, Multiple Sclerosis Laboratory, Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ.
October 1990 - September 1991
Research Assistant. Department of Medicine, Charing Cross and Westminster Medical School, St. Dunstan's Road, Hammersmith, London, W6 8RP.
October 1987 - September 1990
Ph.D Student (MRC Funded). Department of Pharmacology, Charing Cross and Westminster Medical School, St. Dunstan's Road, Hammersmith, London, W6 8RP.
August 1985 - July 1986
Sandwich Student. Applied Physiology Division, Institute of Naval Medicine, Alverstoke, Hampshire. Lung function laboratory operator; thermal and exercise physiology studies on naval ratings.

ACADEMIC QUALIFICATIONS

January 1992:	Ph.D.	Faculty of Science, University of London Thesis entitled "The Influence of Glucocorticoids on the Expression of Lipocortins 1,2 and 5 in the Brain and Pituitary Gland of the Rat
July 1987:	B.Sc.	Honours Degree in Applied Biological Sciences (Upper Second Class) University of the West of England (formerly Bristol Polytechnic)
1983		Four 'A' Levels
1978		Eight 'O' Levels

INVITED TALKS

Open University, 5 May 2003, Milton Keynes, UK.
Symposium: Relevance of cell death in development and disease of the brain. Charité Hospital, Humboldt University 24-25 February 2003, Berlin, Germany.
Cambridge University Department of Neurology, 10 December 2002, Cambridge, UK.
3rd European School of Neuroimmunology, 11-14 September 2002, Tampere, Finland.
British Inflammation Research Association 3-4 July 2002, Bath, UK.
Euroglia 21-25 May 2002, Rome, Italy.

PUBLICATIONS

Groom A.J., **Smith T.**, Turski L. (2003). Multiple sclerosis and glutamate. Ann N Y Acad Sci. 993:229-75; discussion 287-8.

Ohgoh M., Hanada T., **Smith T.**, Hashimoto T., Ueno M., Yamanishi Y., Watanabe M. and Nishizawa Y. (2002). Altered expression of glutamate transporters in experimental autoimmune encephalomyelitis. J. Neuroimmunol. 125: 170-178.

Banati R.B., Newcombe J., Gunn R.N., Cagnin A., Turkheimer F., Heppner F., Price G., Wegner F., Giovannoni G., Miller D.H., Perkin G.D., **Smith T.**, Hewson A.K., Bydder G., Kreutzberg G.W., Jones T., Cuzner M.L. and Myers R. (2000). The peripheral benzodiazepine binding site in the brain in multiple sclerosis: quantitative in vivo imaging of microglia as a measure of disease activity. Brain 123:2321-2337.

Smith T., Groom A., Zhu B. and Turski L. (2000). Autoimmune encephalomyelitis ameliorated by AMPA antagonists. Nature Medicine 6: 62-66.

Folcik V.A, **Smith T.**, O'Bryant S., Kawczak J.A., Zhu B., Sakuri H., Kajiwara A., Staddon J.M., Glabinski A., Chernosky A.L. Tani M., Johnson J.M., Tuohy V.K., Rubin L.L. and Ransohoff R.M. (1999). Treatment with BBB022A or rolipram stabilizes the blood-brain barrier in experimental autoimmune encephalomyelitis: an additional mechanism for the therapeutic effect of type IV phosphodiesterase inhibitors. J. Neuroimmunol. 97: 119-128.

Smith T., Hewson A.K., Kingsley C.I., Leonard J.P. and Cuzner M.L. (1997). Interleukin-12 induces relapses in experimental allergic encephalomyelitis in the Lewis rat. Am. J. Pathol. 150: 1909-1917.

Leonard J.P., Waldburger K.E., Schaub R.G., **Smith T.**, Hewson A.K., Cuzner M.L. and Goldman S.J. (1997). Regulation of the inflammatory response in animal models of multiple sclerosis by interleukin-12. Crit. Rev. Immunol. 17: 545-553.

Smith T., Schmeid M., Hewson A.K., Lassmann H. and Cuzner M.L. (1996). Apoptosis of T-cells and macrophages in the central nervous system of intact and adrenalectomised Lewis rats during experimental allergic encephalomyelitis. J. Autoimmun. 9: 167-174.

Storch M.K., Fischer-Colbrie R., **Smith T.**, Rinner W.A., Hickey W.F., Cuzner M.L., Winkler H and Lassmann H. (1996). Co-localization of secretoneurin immunoreactivity and macrophage infiltration in the lesions of experimental autoimmune encephalomyelitis. Neuroscience 71:885-893.

Hewson A.K., **Smith T.** and Cuzner, M.L. (1995). Suppression of experimental allergic encephalomyelitis in the Lewis rat by the matrix metalloprotease inhibitor Ro31-9790. Inflamm. Res. 44:345-349.

Smith S.F., Benjamin J., Dewar A., Sheppard M., Fox B., **Smith T.**, Guz A. and Tetley T.D. (1995). Effect of dexamethasone on carrageenin-induced inflammation in the lung. Med. Inflamm. 4: 273-281.

Smith S.F., Tetley T.D., Datta A.K., **Smith T.**, Guz A. and Flower R.J. (1995). Lipocortin-1 distribution in bronchoalveolar lavage from healthy human lung: effect of prednisolone. J. Appl. Physiol. 79: 121-128.

Smith T., Hewson A.K., Quarrie L., Leonard J.P. and Cuzner M.L. (1994). Hypothalamic PGE_2 and cAMP production and adrenocortical activation following intra-peritoneal endotoxin injection: *in vivo* microdialysis studies in Lewis and Fischer rats. Neuroendocrinol. 59: 396-405.

Smith T. and Cuzner M.L. (1994). Neuroendocrine-immune interactions in homeostasis and autoimmunity. Neuropathol. Appl. Neurobiol. 20: 413-422.

Smith T., Flower R.J. and Buckingham J.C. (1993). Lipocortins 1,2 and 5 in the central nervous system and pituitary gland of the rat: selective induction by dexamethasone of lipocortin 1 in the anterior pituitary gland. Mol. Neuropharmacol. 3: 45-55.

Invited book chapters

Smith T. and Hewson A.K. (1997). Neuroendocrine-induced immune modulation and autoimmunity. In the Handbook of Immune Modulating Agents. Editor Kresina, T.F. pp 363-383. Marcell Dekker Inc. NY.

Cuzner M.L. and **Smith T.** (1995). Immune responses in the central nervous system in inflammatory demyelinating disease: in Immune Responses in the Nervous System. The Molecular and Cellular Neurobiology Series. Editor Rothwell, N.J. pp 117-142. βios Scientific Publishers.

Buckingham J.C., **Smith T.** and Loxley H.D. (1991). The control of ACTH Secretion: in The Adrenal Gland (second edition). Comprehensive Endocrinology (revised series). Editor James, V.H.T. pp. 131-158. London: Raven Press.

EXHIBIT B

CURRICULUM VITAE

Name:	Prof. Dr. med. LA Turski MD
Date and place of birth:	August 10, 1955, Opole-Lubelskie, Poland
Marital status:	Married to Prof. Dr. med. C Ikonomidou, MD (Greek/German) since October 12, 1985
Nationality:	German
Children:	Christopher Andreas Turski (December 3, 1986) Gabrielle Nicole Turski (April 25, 1990) Jennifer Sabrina Turski (June 22, 2000)
Business address:	Solvay Pharmaceuticals bv C.J. van Houtenlaan 36 NL-1381 CP Weesp The Netherlands E-mail: Les.Turski@solvay.com; LTurski@aol.com
Home address:	Prof. Dr. med. L. Turski Jörsstr. 16 D-13505 Berlin

Education:

Primary school

1961-1969:	Primary school No. 2 in Opole-Lubelskie, Poland

Secondary school

1969-1972:	Adam-Mickiewicz Gymnasium in Opole-Lubelskie, Poland

Graduate school

1972-1978:	Lublin Medical School, Poland
1980:	MD Lublin Medical School, Poland Thesis title: Central action of kainic acid in rats
1988:	PhD Georg-August-University Göttingen, Germany Thesis title: The convulsant action of pilocarpine in rats: Pharmacological, electroencephalographic and morphological analysis of the role of cholinergic mechanisms in epileptogenesis

Clinical training:

1978-1981:	Resident, Internal Medicine, Department of Internal Medicine, Lublin Medical School, Poland

Management training:

1997:	University of Michigan Business School, Ann Arbor, MI, USA

Licensure and certifications:

1978:	Polish Medical Licence
1993:	German Medical Licence (22.09.1993)
1994:	German Board of Pharmacology and Toxicology
1997:	German Board of Clinical Pharmacology

Positions held:

1978-1981:	Resident in Pharmacology and Toxicology at the Institute of Clinical Pathology, Department of Pharmacology, Lublin Medical School, Poland
1978-1981:	Resident in Internal Medicine at the Institute of Internal Medicine, Department of Gastroenterology, Lublin Medical School, Poland
1981-1983:	Postdoctoral Fellow with K Kuschinsky MD, Department of Biochemical Pharmacology, Max-Planck-Institute for Experimental Medicine, Göttingen, Germany
1983-1984:	Postdoctoral Fellow with K-H Sontag PhD, Max-Planck-Institute for Experimental Medicine, Göttingen, Germany
1984:	Postdoctoral Fellow with BS Meldrum MD, Department of Neurology, Institute of Psychiatry, University of London, London SE5 8AF, UK
1985-1987:	Assistant Professor, Max-Planck-Institute for Experimental Medicine, Göttingen, Germany
1984-1988:	Assistant Professor of Pharmacology, Department of Pharmacology, Institute of Clinical Pathology, Lublin Medical School, Poland
1988-1993:	Associate Professor of Neuropharmacology, Department of Pharmacology and Toxicology, Georg-August-University, Göttingen, Germany
1993-	Professor of Pharmacology, Department of Pharmacology and Toxicology, Georg-August-University, Göttingen, Germany
1987-1997:	Head of Experimental Neurology, Research

	Laboratories of Schering AG, Berlin, Germany
1997-1999:	Director of Pharmacology, University College London,
	Eisai London Research Laboratories, London, UK
1999-2001:	Head of Research, Solvay Pharmaceuticals bv, Weesp, The Netherlands
2001-	Vice President Global Discovery, Solvay Pharmaceuticals bv, Weesp, The Netherlands and Solvay Pharmaceuticals GmbH, Hannover, Germany

Fellowships and scholarships:

1. Fellowship - European Training Programme in Brain and Behaviour Research - France (Strasbourg) - 1981
2. Fellowship - Max-Planck-Society Fellowship for Visiting Scientists, 1981-1983

Memberships in professional societies:

German Society of Pharmacology and Toxicology
International Basal Ganglia Society
Society for Neuroscience

Honors and awards:

1972	Scapula aurea awarded by the Lublin Medical School
1977	Award of the Student Scientific Association, Poznan Medical School, Poland
1978	Award of the Student Scientific Association, Katowice, Silesian Medical School, Poland
1983	Award of the Minister of Health and Public Care for Research Achievements, Warsaw, Poland (1st Prize)
1984	1st Prize of the Polish Academy of Sciences, Warsaw, Poland
1985-1986	Michael Prize for Epilepsy Research, Jerusalem, Israel

L Turski

PUBLICATIONS

Department of Pharmacology
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1. Rechberger T, Turski L, Turski W, Wojcik E (1979) The influence of atropine on the antiamphetaminic action of fluphenazine. Ann Univ M Curie-Sklodowska (Lublin) Sectio D 34: 333-339

2. Kleinrok Z, Czuczwar SJ, Turski L (1980) Prevention of kainic acid-induced seizure-like activity by antiepileptic drugs. Pol J Pharmacol Pharm 32: 261-264

3. Kleinrok Z, Czuczwar SJ, Turski L, Zarkowski A (1980) Effect of intracerebroventricular injection of kainic acid on electrically and chemically induced convulsions in mice. Pol J Pharmacol Pharm 32: 265-269

4. Kleinrok Z, Turski L, Wawrzyniak M, Cybulska R (1980) The locomotor and exploratory activities in rats after lesion of hippocampal pyramidal cells with kainic acid. Pol J Pharmacol Pharm 32: 625-637

5. Kleinrok Z, Turski L (1980) Kainic acid-induced wet dog shakes in rats. The relation to central neurotransmitters. Naunyn-Schmiedeberg's Arch Pharmacol 314: 37-46

6. Turski L, Kleinrok Z (1980) Effects of kainic acid on body temperature of rats. Role of catecholaminergic and serotonergic systems. Psychopharmacology 71: 35-39

7. Turski L, Turski W, Czuczwar SJ, Kleinrok Z (1981) Effects of morphine and nalorphine on kainic acid-induced hypothermia in rats. Psychopharmacology 72: 211-214

8. Czuczwar SJ, Turski L, Kleinrok Z (1981) Atropine reversal of kainic acid-induced decrease in the leptazol convulsive threshold. J Pharm Pharmacol 33: 44-45

9. Kleinrok Z, Turski L, Wawrzyniak M, Cybulska R (1981) The locomotor and stereotypy response to dopaminergic drugs and caffeine after intracerebroventricular kainic acid in rats. Pol J Pharmacol Pharm 33: 149-159

10. Kleinrok Z, Turski L (1981) Biochemical consequences of kainic acid injection into the lateral brain ventricle in rat. Acta Bioch Pol 28: 111-122

11. Czuczwar SJ, Turski L, Turski W, Kleinrok Z (1981) Effects of some antiepileptic drugs in pentretrazol-induced convulsions in mice lesioned with kainic acid. Epilepsia 22: 407-414

12. Czuczwar SJ, Turski L, Kleinrok Z (1981) Diphenylhydantoin potentiates the protective effect of diazepam against pentylenetetrazol but not against bicuculline and isoniazid-induced seizures in mice. Neuropharmacology 20: 675-679

13. Czuczwar SJ, Turski L, Turski W, Kleinrok Z (1981) Effect of combined treatment of phenytoin with diazepam on the susceptibility of mice to electroconvulsions. J Pharm Pharmacol 33: 672-673

14. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1981) Studies of carbachol-induced wet-dog shake behaviour in rats. Psychopharmacology 73: 81-83

15. Turski L, Turski W, Czuczwar SJ, Kleinrok Z (1981) Evidence against the involvement of serotonergic mechanisms in wet dog shake behaviour induced by carbachol chloride in rats. Psychopharmacology 73: 376-380

16. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1981) Effect of antidepressant drugs on carbachol chloride-induced wet dog shake behaviour in rats. Neuropharmacology 20: 1193-1196

17. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1981) Effect of trazodone, mianserin, iprindole and zimelidine on wet dog shakes produced by carbachol in rats. J Pharm Pharmacol 33: 670-671

18. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1981) Shuttle behaviour in rats after lesion of hippocampal pyramidal cells with kainic acid. Meth Find Exptl Clin Pharmacol 3: 361-366

19. Turski W, Turski L, Czuczwar SJ, Kleinrok Z (1981) (RS)-α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid: Wet dog shakes, catalepsy and body temperature changes in rats. Pharm Bioch Behav 15: 546-549

20. Czuczwar SJ, Turski L, Kleinrok Z (1981) Effects of morphine, nalorphine and morphine withdrawal on lethal toxicity of intracerebroventricu-lar kainic acid in mice. Pol J Pharmacol Pharm 33: 611-614

21. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1982) Induction of wet dog shakes by intracerebroventricular bethanechol in rats. Antagonism by neurotransmitter receptor blockers. Pharmacology 24: 105-110

22. Turski W, Czuczwar SJ, Turski L, Kleinrok Z (1982) The involvement of catecholaminergic mechanisms in the appearance of wet dog shakes produced by carbachol chloride in rats. Arch int Pharmacodyn Ther 255: 204-211

23. Turski L, Czuczwar SJ, Turski W, Sieklucka-Dziuba M, Kleinrok Z (1982) Diphenylhydantoin enhancement of diazepam effects on locomotor activity in mice. Psycharmacology 76: 198-200

24. Czuczwar SJ, Turski L, Kleinrok Z (1982) Effects of combined treatment with diphenylhydantoin and different benzodiazepines on pentylenetetrazol- and bicuculline-induced seizures in mice. Neuropharmacology 21: 563-567

25. Turski W, Czdczwar SJ, Turski L, Kleinrok Z (1982) Bilateral injection of kainic acid into the rat striatum potentiates morphine, arecoline and pilocarpine but not haloperidol catalepsy. Meth Find Exptl Clin Pharmacol 4: 287-291

26. Czuczwar SJ, Turski L, Turski W, Kleinrok Z (1982) Convulsant action of pentetrazol in rats with selective lesions of the hippocampal pyramidal cells with intracerebroventricular kainic acid. Meth Find Exptl Clin Pharmacol 4: 293-298

27. Turski L, Havemann U, Kuschinsky K (1982) Evidence for functional interactions of morphine in substantia nigra and striatum, in relation to muscular rigidity in rats. Neurosci Lett 28: 291-196

28. Turski L, Havemann U, Kuschinsky K (1982) Evidence that opioid receptors in the substantia nigra pars reticulata are relevant in regulating the function of striatal efferent pathways. Behav Brain Res 5: 415-422

29. Havemann U, Turski L, Kuschinsky K (1982) Role of gabaergic mechanisms in the substantia nigra pars reticulata in modulating morphine-induced muscular rigidity in rats. Neurosci Lett 31: 25-30

30. Turski W. Czuczwar SJ, Turski L, Kleinrok Z (1982) Effect of glutamic acid diethylester on (RS)-α-amino-3-hydroxy-5-ethyl-4-isoxazolepropionic acid- and kainic acid-induced changes of body temperature in rats. Pol J Pharmacol Pharm 34: 161-167

31. Czuczwar SJ, Turski L, Kleinrok Z (1982) Anticonvulsant action of phenobarbital, diazepam, carbamazepine, and diphenylhydantoin in the electroshock test in mice after lesion of hippocampal pyramidal cells with intracerebroventricular kainic acid. Epilepsia 23: 377-382

32. Havemann U, Turski L, Kuschinsky K (1982) Role of opioid receptors in the substantia nigra in morphine-induced muscular rigidity. Life Sci 31: 2319-2322

33. Turski L, Havemann U, Schwarz M, Kuschinsky K (1982) Disinhibition of nigral GABA output neurons mediates muscular rigidity elicited by striatal opioid receptor stimulation. Life Sci 31: 2327-2330

34. Turski L, Havemann U, Kuschinsky K (1982) On the possible role of excitatory amino acids in the striatum in mediating morphine-induced muscular rigidity. Pharm Bioch Behav 17: 715-719

35. Turski L, Schwarz M, Sontag K-H (1982) Interaction between phenytoin and diazepam in mutant Han-Wistar rats with progressive spastic paresis. Naunyn-Schmiedeberg's Arch Pharmacol 321: 48-51

36. Czuczwar SJ, Turski L, Kleinrok Z (1982) Diphenylhydantoininduced potentiation of the anticonvulsant effect of diazepam against some types of experimental seizures. Wiss Zeit Humboldt Univ (Berlin) Math-Nat R 31: 493-494

37. Kleinrok Z, Turski L, Czuczwar SJ, Turski W (1982) Carbacholinduced wet dog shakes - A model for studying antidepressant drugs? Wiss Zeit Humboldt Univ (Berlin) Math-Nat R 31: 519-521

38. Turski WA, Cavalheiro EA, Turski L, Kleinrok Z (1983) Intrahippocampal bethanechol in rats: Behavioural, electroencephalographic and neuropathological correlates. Behav Brain Res 7: 361-370

39. Schwarz M, Turski L, Janiszewski W, Sontag K-H (1983) Is the muscle relaxant effect of diazepam in spastic mutant rats mediated through GABA-independent benzodiazepine receptors? Neurosci Lett 36: 175-180

40. Turski L, Havemann U, Kuschinsky K (1983) The role of the substantia nigra in motility of the rat. Muscular rigidity, body asymetry and catalepsy after injection of morphine into the nigra. Neuropharmacology 22: 1039-1048

41. Schwarz M, Turski L, Sontag K-H (1983) Reversal of the muscle relaxant effect of diazepam but not of progabide by a specific benzodiazepine antagonist: Ro 15-1788. Eur J Pharmacol 90: 139-142

42. Turski WA, Czuczwar SJ, Kleinrok Z, Turski L (1983) Does morphine withdrawal produce brain damage in rats? Life Sci 33: S397-S400

43. Turski WA, Czuczwar SJ, Kleinrok Z, Schwarz M, Turski L (1983) Intraamygdaloid morphine produces seizures and brain damage in rats. Life Sci 33: S615-S618

44. Turski L, Havemann U, Kuschinsky K (1983) Reversal of the muscle relaxant effect of diazepam by the specific benzodiazepine antagonist Ro 15-1788: An electromyographic study in morphine model of muscular rigidity in rats. Life Sci 33: S755-S758

45. Havemann U, Turski L, Schwarz M, Kuschinsky K (1983) Nigral GABAergic mechanisms and EMG activity in rats: Differences between pars reticulata and pars compacta. Eur J Pharmacol 92: 49-56

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